IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	H. William BOSCH et al.
Title:	LIQUID DOSAGE COMPOSITIONS OF STABLE NANOPARTICULATE ACTIVE AGENTS
Appl. No.:	10/619,539
Filing Date:	7/16/2003
Examiner:	Susan T. Tran
Art Unit:	1615
Confirmation Number:	6324

APPEAL BRIEF

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Sir:

Under the provisions of 37 C.F.R. § 41.37, this Appeal Brief is being filed together with a credit card payment form in the amount of $540.00 covering the 37 C.F.R. § 41.20(b)(2) appeal fee. If this fee is deemed to be insufficient, authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 19-0741.

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STATUTES

REAL PARTY IN INTEREST

The real party in interest in this appeal is Elan Pharma International, Ltd., which is the assignee of the present application as recorded at Reel/Frame numbers 015072/0837.

RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are pending.

STATUS OF CLAIMS

Claims 4, 36, 38, 40, 42, 53 and 83 are canceled.

Claims 1-3, 5-35, 37, 39, 41, 43-52, 54-82, 84-123 are pending in the application, with claims 46-52, 54-82, 84-123 withdrawn from consideration. The claims under examination and the withdrawn claims are related as product and process claims. Therefore, the withdrawn process claims are subject to a rejoinder upon allowance of the corresponding product claims.

Claims 1-3, 5-35, 37, 39, 41, 43-45 are finally rejected, and are the subject of this appeal. The pending claims are presented in Appendix A of this Brief.

STATUS OF AMENDMENTS

No claim amendments were made in the response to final Office Action, filed on December 18, 2008. In the final Office Action dated October 8, 2008, the Examiner indicated entry and consideration of an amendment filed July 3, 2008. No other amendments or submissions are pending in the application.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 is to be argued in the brief. The citation to the specification is shown in the parenthesis.

Independent claim 1 reads as follows:

1. A stable nanoparticulate liquid dosage composition **{p. 8, ll. 2-3, 24-25}** comprising:

(a) particles of at least one active agent having an effective average particle size of less than 2000 nm **{p. 8, ll. 3-4, 25-26; p. 30, ll. 5-7}**;

(b) at least one surface stabilizer **{p. 8, ll. 4, 26-27}**;

(c) at least one osmotically active crystal growth inhibitor **{p. 8, ll. 5, 27-28}**that is capable of preventing crystal growth of the active agent **{p. 28, ll. 15-17}** at ambient temperature **{p. 28, ll. 18-19}**, wherein the osmotically active crystal growth inhibitor is selected from the group consisting of glycerol **{p. 8, l. 7; p. 28, l. 18}**, propylene glycol **{p. 28, ll. 18-19}**, mannitol **{p. 8, l. 7; p. 28, l. 19}**, sucrose **{p. 28, l. 20}**, glucose **{p. 28, l. 20}**, fructose **{p. 28, l. 20}**, mannose **{p. 28, l. 20}**, lactose **{p. 28, l. 20}**, xylitol **{p. 28, l. 20}**, sorbitol **{p. 28, l. 20}**, trehalose **{p. 28, l. 20}**, a polysaccharide **{p. 28, l. 21}**, a mono-polysaccharide **{p. 28, l. 21}**, a di-polysaccharides **{p. 28, l. 21}**, a sugars **{p. 28, l. 21}**, a sugar alcohol **{p. 28, l. 21}**, sodium chloride **{p. 8, l. 7; p. 28, l. 22}**, potassium chloride **{p. 28, l. 22}**, magnesium chloride **{p. 28, l. 22}**, and an ionic salt **{p. 28, ll. 22-23}**; and

(d) a liquid media **{p. 8, l. 30}**,

wherein the liquid dosage composition does not incorporate a cloud point modifier **{p. 6, ll. 7-24; p. 7, ll. 24-29; p. 9, ll. 8-9}**.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The first rejection to be reviewed on appeal is the rejection of claims 1-4, 6, 8-24, 26-30, 32-35, 37, 39, 41 and 43-45 under 35 U.S.C. § 103(a) over U.S. Patent No. 6,267,989 to Liversidge, in view of U.S. Patent Application Publication No. 2002/0142050 by Straub et al.

The second rejection to be reviewed on appeal is the rejection of claims 1-6, 8-10, 12, 14-15, 17, 21-24, 26-30 and 32-45 under 35 U.S.C. § 103(a) over U.S. Patent No. 5,665,331 to Bagchi et al., in view of U.S. Patent No. 5,834,025 to De Garavilla et al. and U.S. Patent Application Publication No. 2002/0142050 by Straub et al.

ARGUMENT

I. Rejection over Liversidge and Straub

The Examiner relies on two references to support the rejection of the claims: (i) Liversidge, for the alleged teaching of preventing crystal growth in compositions comprising a nanoparticulate drug, surface stabilizers, and optionally, adjuvants (final Office Action dated October 8, 2008, page 2, second paragraph); and (ii) Straub, for the alleged teaching of using sugar (e.g. mannitol) to inhibit crystal growth (*Id*, page 3, first paragraph). The Examiner's logic to support the rejection is based upon the following statements:

1. The Examiner states: "Liversidge does not expressly teach the [claimed] crystal growth inhibitor." (*Id*, page 2, last paragraph). "Nothing in Liversidge preclude[s] the addition of mannitol as a wetting agent or dispersing agent." Page 2, third paragraph of Advisory Action.

2. The Examiner also makes the statements: "It is well-known in the art that mannitol can be used as a dispersing agent or wetting agent," and "Mannitol is known in the art as a wetting and/or dispersing agent." Page 2 and 4, of the Advisory Action.

3. The Examiner then cites to Straub as teaching the use of a sugar as an anti-crystallization agent. *See* final Office Action, page 3, first paragraph.

Based on the above statements, the Examiner then concludes that it would have been obvious to add a wetting or dispersing agent such as the sugar mannitol, (which is well-known in the art) to Liversidge's composition because Liversidge does not preclude the addition of a wetting agent or dispersing agent. What is then inferred by this statement is that now added mannitol, which was added to Liversidge because it is a wetting or dispersing agent, will now be recognized by one skilled in the art as anti-crystallization agent, as taught by Straub. *See* final Office Action, page 3, first paragraph.

The rejection is in error because 1) the Examiner's statements are flawed, and 2) one skilled in the art would not have had any reason to combine the teachings Straub into Liversidge because Liversidge clearly states that the problem of crystal growth has already been solved, thereby negating any reason one might have to add a crystal growth inhibitor to Liversidge's composition.

As a result, the primary disagreement between Appellants and the Examiner is the ultimate legal determination of obviousness under 35 U.S.C. §103(a), making the record ripe for appeal. Appellants request the Board to resolve the disagreement by reversing the Examiner's rejection in whole for the following more specific reasons.

A. Mannitol is not known as a dispersion or wetting agent.

In the Advisory Action, the Examiner states "It is well-known in the art that mannitol can be used as a dispersing agent and/or wetting agent." Page 2. This statement is repeated at page 4, "Mannitol is known in the art as a wetting and/or dispersing agent."

For the Board's benefit, the Examiner has made this assertion for the first time in the Advisory Action. Such an assertion was not made when prosecution was open. Nevertheless, Appellant provides evidence that shows that this statement is in error.

The evidence to support the Appellant's conclusion is already of record. It is contained within the art cited by the Examiner, namely Straub. Straub discusses wetting agents at ¶¶[0089]-[0093]. Mannitol is conspicuously absent from this list. Straub, as pointed out by the Examiner, characterizes sugars, including mannitol, as "as a bulking agent or as an anti-crystallization agent for drugs in the amorphous state," not as a wetting agent ¶[0082].

Appellants note that ¶[0074] may lead to some confusion. In ¶[0074] Straub states "The matrices may contain hydrophilic or hydrophobic excipients such as polymers, including water soluble polymers, amino acids or sugars which can serve as bulking agents or as wetting agents,

wetting agents such as surfactants, amino acids or sugars, preservatives and tonicity agents." In addition to being grammatically confusing, the sentence is also in conflict with ¶¶[0089]-[0093] which describ in detail the function of and provide examples of, wetting agents. Mannitol is absent from the detailed discussion of wetting agents.

Moreover, Straub points to the knowledge of one skilled in the art to identify known wetting agents, which mannitol is not. At ¶[0091], Straub states: "Most of these wetting agents are known pharmaceutical excipients and are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 1986)."

Although Appellant does not have the 1986 version, Appellant does enclose an excerpt of the 5th Edition of the Handbook of Pharmaceutical Excipients (2006). This publication does not categorize the functional attributes of mannitol as a wetting agent. See for example the mannitol entry and the SLS entry, where SLS is a known wetting agent and is classified as such.

Thus, mannitol is not well-known as wetting or dispersing agent.

B. Liversidge teaches that addition of "other substances" may affect crystal growth

The Examiner states at page 2 of the Advisory Action, "although Liversidge cautions that the addition of other substances may affect crystal growth, Liversidge teaches the addition of pharmaceutically acceptable adjuvants such as wetting agent, and dispersing agent." The Examiner acknowledges that Liversidge may allow addition of substances like wetting or dispersing agents to the composition. And at the same time, the Examiner acknowledges that Liversidge cautions that the addition of other substances should be avoided.

Appellant has established above that mannitol is not a wetting or dispersing agent. It, according to the cited references, is an "other substance." Considering the above-quoted acknowledgement by the Examiner, Liversidge cautions one about the addition of "other

substances" because they may affect crystal growth. One skilled in the art would have therefore have no reason to add the mannitol of Struab into the composition of Liversidge because mannitol (according to the cited art) is an "other substance," which may affect crystal growth.

Appellant cautions the Board not to be duped by the Examiner's flawed logic. The Examiner states: "[n]othing in Liversidge preclude[s] the addition of mannitol as a wetting agent or dispersing agent" (Advisory Action dated February 10, 2009, the paragraph bridging pages 2 and 3). This statement is only partially accurate. The accurate part is that nothing in Liversidge precludes one skilled in the art from addition a wetting agent or dispersing agent. The inaccurate part is that mannitol is not a wetting agent or dispersing agent as shown above.

Given the fundamental flaw in the Examiner's support of the rejection, that mannitol is a wetting or dispersing agent, the logic behind the rejection fails. The Board is respectfully requested to reverse the rejection.

C. The problem of crystal growth has already been solved in Liversidge

Even assuming the Examiner's statements in support of the rejection are factually accurate, the rejection still fails based on the following. Appellant asserts that if a primary prior art reference identifies a problem and provides a solution to that problem, there is no reason for one of ordinary skill in the art to look to a secondary reference to re-solve the already-solved problem.

In the instant rejection, the primary reference, Liversidge, identified crystal growth as a problem in the art. Liversidge explicitly states that "[a]ll of these various prior art methods share one common feature: they require an additional substance added to the nanoparticulate formulation to inhibit or prevent crystal growth and particle aggregation of the nanoparticulate composition. The addition of such a substance can be ***detrimental*** as it may induce ***adverse effects***, particularly for injectable formulations. Moreover, cloud point and crystal growth modifiers are often highly toxic. Thus, this minimizes the usefulness of such substances in

pharmaceutical compositions. In addition, the requirement of an additional substance to obtain a stable composition ***increases production costs***" (column 3, lines 6-16; emphasis added).

Liversidge solves the art-recognized problem of crystal growth and particle aggregation in nanoparticulate active agent compositions by reducing the particle size to less than 400 nm. See claim 1 of Liversidge.

Ignoring the successful solution identified by Liversidge, the Examiner proceeds to cite to a secondary reference, Straub, which is cited for solving the crystal growth problem through the addition "of sugar such as mannitol to inhibit crystal growth for drugs in an amorphous or crystalline state" (final Office Action, page 3, lines 1-2). Straub is the very art that Liversidge expressly distinguishes itself from. Straub requires additional substances added to the formulation to inhibit or prevent crystal growth. Liversidge says it does not. Accordingly, Appellant finds no reason for one of ordinary skill in the art to add a crystal growth inhibitor of Straub to Liversidge when Liversidge has already solved the problem of crystal growth without the need for a crystal growth inhibitor.

II. Rejection over Bagchi, De Garavilla and Straub

The Examiner alleges that Bagchi teaches nanoparticles having an average particle size of less than 300 nm and comprising a pharmaceutical active agent, one or more surface stabilizers, and a crystal growth modifier (final Office Action, the paragraph bridging pages 4 and 5). Straub and De Garavilla are cited for the alleged teachings of sugar as a crystal growth inhibitor and use of two or more surface modifiers, such as glycerol, respectively (*Id*, page 5, third and fourth full paragraph).

Appellants disagree with the Examiner on whether a *prima facie* case of obviousness has been established in accordance with 35 U.S.C. §103(a), and therefore, request the Board to reverse the Examiner's rejection in whole for the reasons detailed below.

A. The reason to substitute the crystal growth inhibitor taught by the secondary references for the crystal growth modifier of Bagchi's composition is lacking.

As submitted in the prior responses filed on July 3, 2008 and on December 18, 2008, respectively, one skilled in the art would not have had any reason to replace Bagchi's crystal growth modifier with either glycerol as taught by De Garavilla or mannitol as taught by Straub.

Bagchi explicitly defines the crystal growth modifier (CGM) as "a chemical that is ***at least 75% identical*** in chemical structure to the pharmaceutical agent" (column 10, lines 54-56; emphasis added). *See* also page 4, lines 15-22. Bagchi refers to the structurally similar crystal growth modifier as "tailor-made" additives and proposes an action mechanism that "[t]ailor-made additives are capable of ***competing directly*** with the host molecule for active sites on the growing crystal surface and by virtue of this competition, slow the overall growth rate of the crystal" (column 12, lines 3-17; emphasis added). Thus, according to Bagchi's rational, other substances that do not share the structure similarity would not be expected to have the specific interaction to compete with the host molecule.

More specifically, Bagchi lays out a selection process of suitable crystal growth modifiers for a target active agent. An active agent to be used is first selected, such as X-ray contrast agent "X." Following this selection, compounds having a chemical structure sharing at least 75% identity with agent "X" are identified as possible candidates for crystal growth modifiers (*see* column 10, line 62, through column 11, line 65). In particular, Bagchi emphasizes that "the CGM compounds are very similar in structure to the X-ray contrast agent 'X', and also contain 3 iodine atoms as does the known contrast agent 'X'" (column 11, lines 56-59).

In advancing the rejection based on Bagchi, De Garavilla and Straub, the Examiner asserts that "Bagchi teaches a wide variety of active agents" and that "the burden is shifted to applicant to show that mannitol or CGM taught by Straub does not share at least 75% identity with any of the listed active agents of Bagchi" (Advisory Action, page 5, lines 17-21). By this assertion, the Examiner appears to have applied a "reversed" rationale of Bagchi by first

identifying the mannitol of Straub or the glycerol of De Garavilla, with the aid of impermissible hindsight, and then attempting to search for an active agent that shares at least 75% identity with mannitol or glycerol.

As discussed *supra*, Bagchi describes identifying an active agent ***first***, followed by selecting a compound that shares at least 75% structural similarity with the active agent as a suitable crystal growth modifier. However, Bagchi does not enable a methodology suggested by the Examiner, which identifies a crystal growth modifier first followed by selection of an active agent that has at least 75% identity with the CGM. As such, the rejection is based on a faulty rationale that lacks any support within the cited art.

Because the Examiner has failed to establish a *prima facie* case of obviousness, the burden remains with the Examiner to articulate a rejection based on the cited art. Accordingly, reversal in whole of the rejection by the Board is respectfully requested.

B. The combined teachings of Bagchi, De Garavilla and Straub would not have resulted in the claimed composition.

Even when the teachings of cited references are combined, one skilled in the art would not have obtained the claimed stable nanoparticulate liquid dosage composition comprising, *inter alia*, particles of at least one active agent having an effective average particle size of less than 2000 nm.

Similar to Liversidge, Bagchi's compositions have a particle size range much narrower than that of the claimed composition. For example, Bagchi describes that the particle size is "less than about 400 nm," or in preferred embodiments, "less than 300 nm," and "less than 250 nm" (abstract; column 6, lines 42 and 48-52; column 12, lines 38-39). Bagchi lacks any teaching that the crystal growth modifier can effectively prevent crystal growth in a nanoparticulate composition having a particle size larger than 400 nm.

Accordingly, the Examiner fails to articulate how the combined teachings of the cited references meet each and every claim limitations. Reversal of the rejection by the Board is warranted, therefore.

CONCLUSION

For the reasons discussed above, Appellants respectfully submit that all pending claims are in condition for allowance, and respectfully requests that the rejections be reversed in whole, and that the claims be allowed to issue.

Respectfully submitted,

Date May 5, 2009

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APPENDIX A: CLAIMS INVOLVED IN APPEAL

1. (Previously Presented) A stable nanoparticulate liquid dosage composition comprising:

(a) particles of at least one active agent having an effective average particle size of less than 2000 nm;

(b) at least one surface stabilizer;

(c) at least one osmotically active crystal growth inhibitor that is capable of preventing crystal growth of the active agent at ambient temperature, wherein the osmotically active crystal growth inhibitor is selected from the group consisting of glycerol, propylene glycol, mannitol, sucrose, glucose, fructose, mannose, lactose, xylitol, sorbitol, trehalose, a polysaccharide, a mono-polysaccharide, a di-polysaccharides, a sugars, a sugar alcohol, sodium chloride, potassium chloride, magnesium chloride, and an ionic salt; and

(d) a liquid media,

wherein the liquid dosage composition does not incorporate a cloud point modifier.

2. (Original) The composition of claim 1, wherein the active agent particles form crystals upon storage or heating in the absence of the crystal growth inhibitor.

3. (Original) The composition of claim 1, wherein the osmotically active crystal growth inhibitor is at least partially water-soluble and does not solubilize the nanoparticulate active agent.

4. (Cancelled)

5. (Previously Presented) The composition of claim 1, wherein the crystal growth inhibitor is glycerol.

6. (Previously Presented) The composition of claim 1, where the crystal growth inhibitor is mannitol.

7. (Previously Presented) The composition of claim 1, where the crystal growth inhibitor is sodium chloride.

8. (Original) The composition of claim 1, wherein the amount of the crystal growth inhibitor present in the liquid dosage form ranges from about 0.1% to about 95% concentration, by weight.

9. (Original) The composition of claim 1, wherein the amount of the crystal growth inhibitor present in the liquid dosage form ranges from about 0.5% to about 90% concentration, by weight.

10. (Original) The composition of claim 1, wherein the effective average particle size of the nanoparticulate active agent particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

11. (Original) The composition of claim 1 or 10, wherein at least about 70%, at least about 90%, or at least about 95% of the active agent particles have a particle size less than the effective average particle size.

12. (Original) The composition of claim 1, wherein the amount of the active agent per ml is equal to or greater than the amount of the active agent per ml of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent.

13. (Original) The composition of claim 1, wherein the liquid media of the liquid dosage composition is selected from the group consisting of water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, and glycol.

14. (Original) The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

15. (Original) The composition of claim 1 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

16. (Original) The composition of claim 1, wherein the at least one active agent is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the active agent and at least one surface stabilizer, not including other excipients.

17. (Original) The composition of claim 1, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the active agent and at least one surface stabilizer, not including other excipients.

18. (Original) The composition of claim 1, wherein the ratio of active agent to a polymeric surface modifier is selected from the group consisting of from about 20:1 to about 1:10, from about 10:1 to about 1:5, and from about 5:1 to about 1:1, by weight.

19. (Original) The composition of claim 1, comprising at least two surface stabilizers.

20. (Original) The composition of claim 19, wherein the ratio of active agent to the second surface stabilizer is selected from the group consisting of from about 500:1 to about 5:1, from about 350:1 to about 10:1, and from about 100:1 to about 20:1, by weight.

21. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

22. (Original) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a polymeric surface stabilizer, a nonionic surface stabilizer, and a zwitterionic surface stabilizer.

23. (Original) The composition of claim 22, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-

D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

24. (Previously Presented) The composition of claim 22, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium

chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

25. (Original) The composition of any of claims 22 or 24, wherein the composition is bioadhesive.

26. (Original) The composition of claim 1, wherein the active agent is selected from the group consisting of a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, and mixtures thereof.

27. (Original) The composition of claim 1, wherein the one or more active agents have a solubility in water selected from the group consisting of less than about 30 mg/ml, less

than about 20 mg/ml, less than about 10 mg/ml, and less than about 1 mg/ml, under ambient conditions.

28. (Original) The composition of claim 1 wherein the active agent comprises anti-inflammatory and analgesic properties.

29. (Original) The composition of claim 1, wherein the at least one active agent is selected from the group consisting of COX-2 inhibitors, anticancer agents, NSAIDS, proteins, peptides, nutraceuticals, anti-obesity agents, corticosteroids, elastase inhibitors, analgesics, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acne medication, alpha-hydroxy formulations, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, and respiratory illness therapies associated with acquired immune deficiency syndrome.

30. (Original) The composition of claim 29, wherein the nutraceutical is selected from the group consisting of dietary supplements, vitamins, minerals, herbs, healing foods that have medical or pharmaceutical effects on the body, folic acid, fatty acids, fruit and vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin,

glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics.

31. (Original) The composition of claim 1, wherein the active agent is selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

32. (Previously Presented) The composition of claim 1, having a viscosity, at a shear rate of 0.1 (1/s), is selected from the group consisting of from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from

about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

33. (Previously Presented) The composition of claim 1, having a viscosity selected from the group consisting of less than about 1/200, less than about 1/100, less than about 1/50, less than about 1/25, and less than about 1/10 of the viscosity of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent at about the same concentration per ml of active agent.

34. (Previously Presented) The composition of claim 1, having a viscosity selected from the group consisting of less than about 5%, less than about 10%, less than about 15%, less than about 20%, less than about 25%, less than about 30%, less than about 35%, less than about 40%, less than about 45%, less than about 50%, less than about 55%, less than about 60%, less than about 65%, less than about 70%, less than about 75%, less than about 80%, less than about 85%, and less than about 90% of the viscosity of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent at about the same concentration per ml of active agent.

35. (Previously Presented) The composition of claim 1, having a T_{max}, when assayed in the plasma of a mammalian subject following administration, less than the T_{max} for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

36. (Cancelled)

37. (Previously Presented) The composition of claim 1, having a C_{max}, when assayed in the plasma of a mammalian subject following administration, greater than the C_{max} for a

conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

38. (Cancelled)

39. (Previously Presented) The composition of claim 1, having an AUC, when assayed in the plasma of a mammalian subject following administration, greater than the AUC for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

40. (Cancelled)

41. (Original) The composition of claim 1 which does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

42. (Cancelled)

43. (Original) The composition of claim 1, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

44. (Original) The composition of claim 43, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC, when administered to a human.

45. (Original) The composition of claim 43, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max}, when administered to a human.

46. (Withdrawn) A method of making a stable nanoparticulate liquid dosage composition comprising contacting particles of at least one active agent with at least one surface

stabilizer in the presence of a liquid media for a time and under conditions sufficient to provide a nanoparticulate active agent composition wherein:

(a) the active agent particles have an effective average particle size of less than 2000 nm; and

(b) at least one osmotically active crystal growth inhibitor is added to the composition either before, during, or after the active agent particle size reduction, wherein the osmotically active crystal growth inhibitor is selected from the group consisting of glycerol, propylene glycol, mannitol, sucrose, glucose, fructose, mannose, lactose, xylitol, sorbitol, trehalose, a polysaccharide, a mono-polysaccharide, a di-polysaccharides, a sugars, a sugar alcohol, sodium chloride, potassium chloride, magnesium chloride, and an ionic salt.

47. (Withdrawn) The method of claim 46, wherein said contacting comprising grinding.

48. (Withdrawn) The method of claim 47, wherein said grinding comprising wet grinding.

49. (Withdrawn) The method of claim 46, wherein said contacting comprises homogenizing.

50. (Withdrawn) The method of claim 46, wherein said contacting comprises:

(a) dissolving the particles of at least one active agent in a solvent;

(b) adding the resulting solution of the active agent to a solution comprising at least one surface stabilizer; and

(c) precipitating the solubilized active agent and at least one surface stabilizer by the addition thereto of a non-solvent.

51. (Withdrawn) The method of claim 46, wherein the active agent particles form crystals upon storage or heating in the absence of the crystal growth inhibitor.

52. (Withdrawn) The method of claim 46, wherein the osmotically active crystal growth inhibitor is at least partially water-soluble and does not solubilize the nanoparticulate active agent.

53. (Cancelled)

54. (Withdrawn) The method of claim 46, wherein the crystal growth inhibitor is glycerol.

55. (Withdrawn) The method of claim 46, where the crystal growth inhibitor is mannitol.

56. (Withdrawn) The method of claim 46, where the crystal growth inhibitor is sodium chloride.

57. (Withdrawn) The method of claim 46, wherein the amount of the crystal growth inhibitor present in the liquid dosage composition ranges from about 0.1% to about 95% concentration, by weight.

58. (Withdrawn) The method of claim 57, wherein the amount of the crystal growth inhibitor present in the liquid dosage composition ranges from about 0.5% to about 90% concentration, by weight.

59. (Withdrawn) The method of claim 46, wherein the effective average particle size of the nanoparticulate active agent particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400

nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

60. (Withdrawn) The method of claim 46 or 59, wherein at least about 70%, about 90%, or about 95% of the active agent particles have a particle size less than the effective average particle size.

61. (Withdrawn) The method of claim 46, wherein the liquid media of the liquid dosage composition is selected from the group consisting of water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, and glycol.

62. (Withdrawn) The method of claim 46, wherein the at least one active agent is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the active agent and at least one surface stabilizer, not including other excipients.

63. (Withdrawn) The method of claim 46, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the active agent and at least one surface stabilizer, not including other excipients.

64. (Withdrawn) The method of claim 46, wherein the ratio of active agent to a polymeric surface modifier is selected from the group consisting of from about 20:1 to about 1:10, from about 10:1 to about 1:5, and from about 5:1 to about 1:1, by weight.

65. (Withdrawn) The method of claim 46, comprising at least two surface stabilizers.

66. (Withdrawn) The method of claim 65, wherein the ratio of active agent to the second surface stabilizer is selected from the group consisting of from about 500:1 to about 5:1, from about 350:1 to about 10:1, and from about 100:1 to about 20:1, by weight.

67. (Withdrawn) The method of claim 46, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a polymeric surface stabilizer, a nonionic surface stabilizer, and a zwitterionic surface stabilizer.

68. (Withdrawn) The method of claim 67, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol,

PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

69. (Withdrawn) The method of claim 67, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl $(ethenoxy)_4$ ammonium chloride, lauryl dimethyl $(ethenoxy)_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl

benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

70. (Withdrawn) The method of claim 46, wherein the active agent is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

71. (Withdrawn) The method of claim 46, wherein the one or more active agents have a solubility in water selected from the group consisting of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, and less than about 1 mg/ml, under ambient conditions.

72. (Withdrawn) The method of claim 46, wherein the active agent comprises anti-inflammatory and analgesic properties.

73. (Withdrawn) The method of claim 46, wherein the at least one active agent is selected from the group consisting of COX-2 inhibitors, anticancer agents, NSAIDS, proteins, peptides, nutraceuticals, anti-obesity agents, corticosteroids, elastase inhibitors, analgesics, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory

agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acne medication, alpha-hydroxy formulations, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, and respiratory illness therapies associated with acquired immune deficiency syndrome.

74. (Withdrawn) The method of claim 73, wherein the nutraceutical is selected from the group consisting of dietary supplements, vitamins, minerals, herbs, healing foods that have medical or pharmaceutical effects on the body, folic acid, fatty acids, fruit and vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics.

75. (Withdrawn) The method of claim 46, wherein the active agent is selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin, cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine,

felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

76. (Withdrawn) A method of treating a subject with a stable nanoparticulate liquid dosage composition comprising administering to the subject an effective amount of a composition comprising:

(a) particles of at least one active agent having an effective average particle size of less than 2000 nm;

(b) at least one surface stabilizer;

(c) at least one osmotically active crystal growth inhibitor, wherein the osmotically active crystal growth inhibitor is selected from the group consisting of glycerol, propylene glycol, mannitol, sucrose, glucose, fructose, mannose, lactose, xylitol, sorbitol, trehalose, a polysaccharide, a mono-polysaccharide, a di-polysaccharides, a sugars, a sugar alcohol, sodium chloride, potassium chloride, magnesium chloride, and an ionic salt; and

(d) a liquid media.

77. (Withdrawn) The method of claim 76, wherein said subject is a human.

78. (Withdrawn) The method of claim 76, wherein the condition to be treated is selected from the group consisting of neoplastic diseases, breast cancer, endometrial cancer, uterine cancer, cervical cancer, prostate cancer, renal cancer, hormone replacement therapy in post-menopausal women, endometriosis, hirsutism, dysmenorrhea, uterine bleeding, HIV wasting, cancer wasting, migraine headache, cachexia, anorexia, castration, oral contraception,

motion sickness, emesis related to cytotoxic drugs, gastritis, ulcers, dyspepsia, gastroenteritis, including collitis and food poisoning, inflammatory bowel disease, Crohn's disease, migraine headaches, and any other condition which is accompanied by the symptoms of nausea and vomiting.

79. (Withdrawn) The method of claim 76, wherein the condition to be treated is selected from the group consisting of pain, inflammation, arthritis, cancer, kidney disease, osteoporosis, Alzheimer's disease, and familial adenomatous polyposis.

80. (Withdrawn) The method of claim 79, wherein the condition to be treated is selected from the group consisting of osteoarthritis, rheumatoid arthritis, juvenile arthritis, gout, ankylosing spondylitis, systemic lupus erythematosus, bursitis, tendinitis, myofascial pain, carpal tunnel syndrome, fibromyalgia syndrome, infectious arthritis, psoriatic arthritis, reiter's syndrome, and scleroderma.

81. (Withdrawn) The method of claim 76, wherein the active agent particles form crystals upon storage or heating in the absence of the crystal growth inhibitor.

82. (Withdrawn) The method of claim 76, wherein the osmotically active crystal growth inhibitor is at least partially water-soluble and does not solubilize the nanoparticulate active agent.

83. (Cancelled)

84. (Withdrawn) The method of claim 76, wherein the crystal growth inhibitor is glycerol.

85. (Withdrawn) The method of claim 76, where the crystal growth inhibitor is mannitol.

86. (Withdrawn) The method of claim 76, where the crystal growth inhibitor is sodium chloride.

87. (Withdrawn) The method of claim 76, wherein the amount of the crystal growth inhibitor present in the liquid dosage composition ranges from about 0.1% to about 95% concentration, by weight.

88. (Withdrawn) The method of claim 76, wherein the amount of the crystal growth inhibitor present in the liquid dosage composition ranges from about 0.5% to about 90% concentration, by weight.

89. (Withdrawn) The method of claim 76, wherein the effective average particle size of the nanoparticulate active agent particles is selected from the group consisting of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 100 nm, less than about 75 nm, and less than about 50 nm.

90. (Withdrawn) The method of claim 76 or 89, wherein at least about 70%, about 90%, or about 95% of the active agent particles have a particle size less than the effective average particle size.

91. (Withdrawn) The method of claim 76, wherein the amount of the active agent per ml is equal to or greater than the amount of the active agent per ml of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent.

92. (Withdrawn) The method of claim 76, wherein the liquid media of the liquid dosage composition is selected from the group consisting of water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, and glycol.

93. (Withdrawn) The method of claim 76, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

94. (Withdrawn) The method of claim 76 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

95. (Withdrawn) The method of claim 76, wherein the at least one active agent is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined weight of the active agent and at least one surface stabilizer, not including other excipients.

96. (Withdrawn) The method of claim 76, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the active agent and at least one surface stabilizer, not including other excipients.

97. (Withdrawn) The method of claim 76, wherein the ratio of active agent to a polymeric surface modifier is selected from the group consisting of from about 20:1 to about 1:10, from about 10:1 to about 1:5, and from about 5:1 to about 1:1, by weight.

98. (Withdrawn) The method of claim 76, comprising at least two surface stabilizers.

99. (Withdrawn) The method of claim 98, wherein the ratio of active agent to the second surface stabilizer is selected from the group consisting of from about 500:1 to about 5:1, from about 350:1 to about 10:1, and from about 100:1 to about 20:1, by weight.

100. (Withdrawn) The method of claim 76, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

101. (Withdrawn) The method of claim 76, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a polymeric surface stabilizer, a nonionic surface stabilizer, and a zwitterionic surface stabilizer.

102. (Withdrawn) The method of claim 101, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-

glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

103. (Withdrawn) The method of claim 101, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, a phospholipid, cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride, C_{12-15}dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride, lauryl dimethyl (ethenoxy)$_4$ ammonium bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride

monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12} trimethyl ammonium bromides, C_{15} trimethyl ammonium bromides, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

104. (Withdrawn) The method of claim 76, wherein the active agent is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

105. (Withdrawn) The method of claim 76, wherein the one or more active agents have a solubility in water selected from the group consisting of less than about 30 mg/ml, less than about 20 mg/ml, less than about 10 mg/ml, and less than about 1 mg/ml, under ambient conditions.

106. (Withdrawn) The method of claim 76, wherein the active agent comprises anti-inflammatory and analgesic properties.

107. (Withdrawn) The method of claim 76, wherein the at least one active agent is selected from the group consisting of COX-2 inhibitors, anticancer agents, NSAIDS, proteins,

peptides, nutraceuticals, anti-obesity agents, corticosteroids, elastase inhibitors, analgesics, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, xanthines, acne medication, alpha-hydroxy formulations, cystic-fibrosis therapies, asthma therapies, emphysema therapies, respiratory distress syndrome therapies, chronic bronchitis therapies, chronic obstructive pulmonary disease therapies, organ-transplant rejection therapies, therapies for tuberculosis and other infections of the lung, and respiratory illness therapies associated with acquired immune deficiency syndrome.

108. (Withdrawn) The method of claim 107, wherein the nutraceutical is selected from the group consisting of dietary supplements, vitamins, minerals, herbs, healing foods that have medical or pharmaceutical effects on the body, folic acid, fatty acids, fruit and vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics.

109. (Withdrawn) The method of claim 76, wherein the active agent is selected from the group consisting of acyclovir, alprazolam, altretamine, amiloride, amiodarone, benztropine mesylate, bupropion, cabergoline, candesartan, cerivastatin, chlorpromazine, ciprofloxacin,

cisapride, clarithromycin, clonidine, clopidogrel, cyclobenzaprine, cyproheptadine, delavirdine, desmopressin, diltiazem, dipyridamole, dolasetron, enalapril maleate, enalaprilat, famotidine, felodipine, furazolidone, glipizide, irbesartan, ketoconazole, lansoprazole, loratadine, loxapine, mebendazole, mercaptopurine, milrinone lactate, minocycline, mitoxantrone, nelfinavir mesylate, nimodipine, norfloxacin, olanzapine, omeprazole, penciclovir, pimozide, tacolimus, quazepam, raloxifene, rifabutin, rifampin, risperidone, rizatriptan, saquinavir, sertraline, sildenafil, acetyl-sulfisoxazole, temazepam, thiabendazole, thioguanine, trandolapril, triamterene, trimetrexate, troglitazone, trovafloxacin, verapamil, vinblastine sulfate, mycophenolate, atovaquone, atovaquone, proguanil, ceftazidime, cefuroxime, etoposide, terbinafine, thalidomide, fluconazole, amsacrine, dacarbazine, teniposide, and acetylsalicylate.

110. (Withdrawn) The method of claim 76, wherein the viscosity of the composition, at a shear rate of 0.1 (1/s), is selected from the group consisting of from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

111. (Withdrawn) The method of claim 76, wherein the viscosity of the composition is selected from the group consisting of less than about 1/200, less than about 1/100, less than about 1/50, less than about 1/25, and less than about 1/10 of the viscosity of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent at about the same concentration per ml of active agent.

112. (Withdrawn) The method of claim 76, wherein the viscosity of the composition is selected from the group consisting of less than about 5%, less than about 10%, less than about 15%, less than about 20%, less than about 25%, less than about 30%, less than about 35%, less than about 40%, less than about 45%, less than about 50%, less than about 55%, less than about 60%, less than about 65%, less than about 70%, less than about 75%, less than about 80%, less than about 85%, and less than about 90% of the viscosity of a standard conventional non-nanoparticulate liquid dosage composition of the same active agent at about the same concentration per ml of active agent.

113. (Withdrawn) The method of claim 76, wherein the T_{max} of the active agent, when assayed in the plasma of a mammalian subject following administration, is less than the T_{max} for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

114. (Withdrawn) The method of claim 113, wherein the T_{max} is selected from the group consisting of not greater than about 90%, not greater than about 80%, not greater than about 70%, not greater than about 60%, not greater than about 50%, not greater than about 30%, not greater than about 25%, not greater than about 20%, not greater than about 15%, and not greater than about 10% of the T_{max}, exhibited by a non-nanoparticulate formulation of the same active agent, administered at the same dosage.

115. (Withdrawn) The method of claim 76, wherein the C_{max} of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{max}

for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

116. (Withdrawn) The method of claim 115, wherein the C_{max} is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the C_{max} exhibited by a non-nanoparticulate formulation of the same active agent, administered at the same dosage.

117. (Withdrawn) The method of claim 76, wherein the AUC of the active agent, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of the same active agent, administered at the same dosage.

118. (Withdrawn) The method of claim 117, wherein the AUC is selected from the group consisting of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, and at least about 100% greater than the AUC exhibited by a non-nanoparticulate formulation of the same active agent, administered at the same dosage.

119. (Withdrawn) The method of claim 76 which does not produce significantly different absorption levels when administered under fed as compared to fasting conditions.

120. (Withdrawn) The method of claim 119, wherein the difference in absorption of the active agent composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

121. (Withdrawn) The method of claim 76, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

122. (Withdrawn) The method of claim 121, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC, when administered to a human.

123. (Withdrawn) The method of claim 121, wherein "bioequivalency" is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max}, when administered to a human.

APPENDIX B: EVIDENCE

1. U.S. Patent No. 6,267,989 to Liversidge
2. U.S. Patent Application Publication No. 2002/0142050 by Straub et al.
3. U.S. Patent No. 5,665,331 to Bagchi et al.
4. U.S. Patent No. 5,834,025 to De Garavilla et al.
5. Excerpt of the Handbook of Pharmaceutical Excipients, 5^{th} *Ed.* (2006)

APPENDIX C: RELATED PROCEEDINGS

No related proceedings are pending.